Inter-limb mechanisms and clinical relevance of cross-education in humans

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Chapter 2

Role of the mirror-neuron system in cross-education

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Abstract

The present review proposes the untested hypothesis that cross-education performed with a mirror increases the transfer of motor function to the resting limb compared with standard cross-education interventions without a mirror. The hypothesis is based on neuroanatomical evidence suggesting an overlap in activated brain areas when a unilateral motor task is performed with and without a mirror in the context of cross-education of the upper extremities. The review shows that the mirror-neuron system (MNS), connecting sensory neurons responding to visual properties of an observed action and motor neurons that discharge action potentials during the execution of a similar action, has the potential to enhance cross-education. After a literature search we narrowed the review to studies that examined healthy young adults who performed unilateral strength training and unilateral motor tasks with or without a mirror and assessed outcome measures in relation to the changes in brain activity, motor cortical excitability, and corticospinal excitability. We have identified six chronic studies that examined the effects of unilateral strength training on neural adaptations and 15 cross-sectional studies that examined acute changes in brain activation, motor cortical and corticospinal excitability using imaging, electroencephalographic, magnetoencephalographic, and magnetic brain stimulation. There were two chronic and nine cross-sectional studies in which participants performed unilateral motor tasks while viewing the image of the active hand superimposed on the resting hand's image. Collectively the data suggest that the MNS is involved in cross-education and the hypothesis is tenable. However, future studies are needed to elucidate the precise mechanism of how the use of a mirror in a cross-education study augments transfer to the non-exercised limb. Recent studies show a strength sparing effect in the immobilized arm after strength training of the free arm in healthy individuals and improved bilateral function after unilateral exercise therapy in stroke patients. It is thus conceptually justified to conduct randomized clinical trials that supplement cross-education protocols with a mirror. Such a treatment could reduce muscle weakness caused by limb fractures, anterior-cruciate ligament reconstruction surgery, stroke, and other unilateral motor dysfunctions.

2.1 Introduction

Imitation is important in human development and for learning motor skills [1]. The functional benefits derived from imitation are based on a mechanism that matches the observed action with an internal motor representation of that action [2,3]. The neuroanatomical basis of this mechanism is the mirror-neuron system (MNS) that connects sensory neurons responding to visual properties of an observed action and motor neurons that discharge action potentials during the execution of a similar action. Active performance of a motor act, observation of a motor act we perform, observation of a motor act someone else performs, imitation of a motor act, viewing a motor act in a mirror, as is often the case in dance and sport practice, and mirror therapy, are signals that activate a specific network of neurons, forming the MNS [4,5]. These neurons reside in the occipital, temporal, and parietal visual areas and in the two frontoparietal motor areas. These latter areas include the rostral part of the inferior parietal gyrus, the lower part of the precentral gyrus, and the posterior part of the inferior frontal gyrus [3,6-8].

A specific form of motor learning in which imitation of the exercising limb might play a role is cross-education. Cross-education is the performance improvement in the contralateral homologous muscle of the untrained limb after a period of unilateral practice of an effortful motor task or skill [9-12]. Previous studies discussed the magnitude of cross-education (0 up to ~80%), the effects of contraction type, speed, and intensity, and the muscle groups exhibiting cross-education (small hand muscles, wrist, elbow, knee, and ankle extensors) [10,11,13-17]. Recent studies show that cross-education following strength training is associated with increases in activation of brain areas that overlap with areas containing mirror neurons [9,13,18]. A recently recognized approach for inducing cross-education is mirror training. In mirror training, a mirror image of the practicing hand is superimposed over the untrained hand [19,20] and such training may improve function in patients (for a review see Thieme et al. [21]; Bowering et al. [22]). There is evidence that the superimposed view of the exercising hand activates elements of the MNS [19,20]. Noijma et al. [20] discuss how the MNS could mediate inter-hemispheric effects relying on the MNS-like properties of the primary motor cortex (M1) and Läppchen et al. [23] mentioned the potential role of the action observation network in mediating cross-education by using a mirror.

The present review examines the idea that the MNS is involved in cross-education and that viewing the exercising hand in a mirror would enhance the magnitude of cross-education. The first aim of this review is to evaluate the role of the MNS in cross-education during unilateral upper extremity strength training. The second aim is to determine the role of the MNS in cross-education during upper extremity mirror training. We address these aims through a literature search that identifies neuroanatomical, imaging, transcranial magnetic stimulation (TMS), magnetoencephalographic (MEG), and electroencephalographic (EEG) studies that examine the acute and chronic effects of unilateral motor practice with or without a mirror on cross-education in the upper extremities. Imaging, MEG, and EEG studies address cortical changes regarding brain activation; TMS studies measure changes in motor cortical (M1) and corticospinal (entire path from M1 to the motoneuron) excitability.

2.1.1 Neuroanatomy of mirror neurons and its relevance to cross-education

Neuroanatomical studies in the macaque monkey (*Simia sylvanus Linnaeus*) revealed that specific population of cortical neurons discharge action potentials when the animals performed a specific motor task and also when they observed a peer performing the same motor task [24,25]. Although observation of a peer executing a task activates mirror neurons, this activation does not result in overt movements. There is now strong behavioural evidence that an analogous system also exists in humans [26-29]. According to the 'simulation theory' [30], movement observation is a covert motor act that activates the same neural substrates as the actual execution, producing subliminal facilitation of neurons forming the motor neural network (for reviews and meta-analyses see Caspers et al. [31]; Grezes and Decety [32]; Jeannerod [30]; Molenberghs et al. [33]; Munzert et al. [34]). TMS studies reported an increase in M1 [34] and corticospinal activation during a direct and mirror observation of a motor act in a task specific manner, co-varying with task complexity [35-40]. Viewing a motor act in a mirror is a specific form of action observation and a focus of the present review.

Mirror neurons are present in a number of cortical areas and form part of a complex network required for processing information associated with imitation of a motor act. There is homology in brain areas in humans and monkeys contributing to the MNS, especially the neurons in the premotor cortex [27,29]. Neurons in the occipital, temporal, and parietal visual areas and the two motor areas form the MNS in humans [6-8]. These two motor areas, also known as the frontoparietal MNS, consist of the rostral part of the inferior parietal gyrus the lower part of the precentral gyrus and the posterior part of the inferior frontal gyrus. Figure 2.1 schematically depicts the MNS. There is communication between elements of the MNS

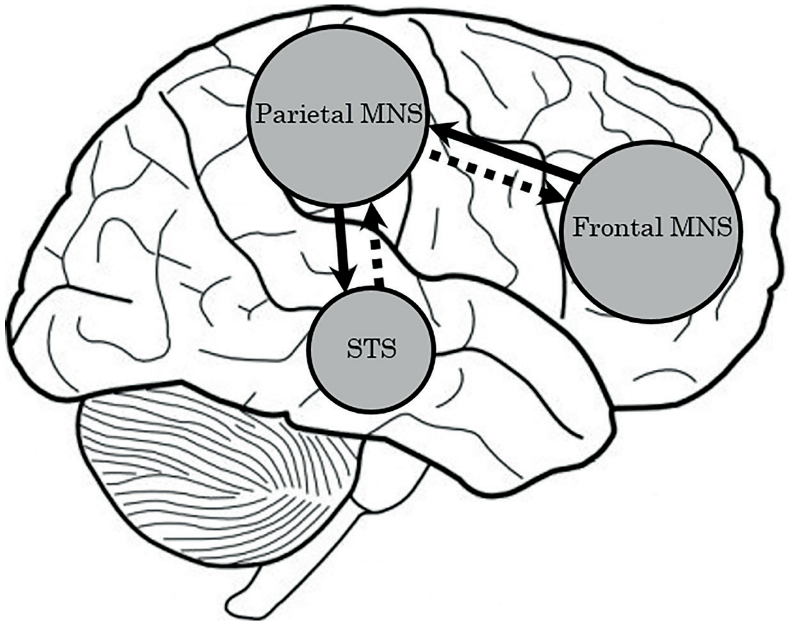

Figure 2.1 | Schematic representation of the core circuitry of the mirror-neuron system on the lateral wall of the right hemisphere based on previous models of the mirror-neuron system.[3,8] Solid and dashed arrows, respectively denote the forward and inverse model. MNS, mirror-neuron system. STS, superior temporal sulcus.

through pathways interconnecting the different brain areas. These interconnecting pathways form the inverse and forward model, in which the inverse model is updated on the basis of the forward model [3,8]. In the inverse model, visual information is processed in the superior temporal sulcus (STS), which provides a higher-order visual description of the observed action. This description is then transmitted from the STS to the frontoparietal portion of the MNS, where the goal of the action and the specific motor program for achieving that action is coded. Lastly and indicated as the forward model, a copy of the motor plan of the observed actions, the 'efference' copy, is transmitted from the frontoparietal MNS regions to the STS, where the predicted sensory consequences of the planned imitative action are compared with the visual description of the observed action [3,8]. This path of activation is present when participants imitate simple or over-learned motor actions [3,8]. Imitation of a novel motor task activates such additional brain areas as the middle frontal gyrus (Brodmann area 46), the dorsal premotor cortex (dPMC), superior parietal gyrus, and the caudal middle frontal gyrus, areas all involved in motor preparation [41]. The activity in the middle frontal gyrus seems to play a role in the selection of the appropriate motor program for the novel action [42]. This role is not specific for the imitation of novel actions because Brodmann area 46 is also active during other forms of sensory-motor behaviour [43]. Thus, imitation of a familiar task activates the MNS, comprising the STS and the frontoparietal areas but additional circuits become active when primates imitate novel actions, including Brodmann area 46 and the three motor preparation areas. There is evidence that adaptations in elements of the MNS as a result of motor learning or training differ between novice and expert dancers and musicians [4]. Of particular importance are the inferior parietal lobule, the ventral premotor cortex, and the caudal portion of the inferior frontal gyrus, forming roughly the 'pars opercularis', lying between the inferior precentral sulcus and the ascending ramus of the lateral sulcus. Covering ('opercularis') the insula, these areas have motor properties and become strongly activated during observing a motor act in a mirror [33]. It is unclear if the dense white matter axon body, giving rise to the transcallosal fibres, is a part of the MNS. Indirect evidence from studies using mirror therapy in patients with a stroke [44] and phantom pain [45], and healthy subjects performing unimanual motor practice [19] suggests that the enlarged activation in the 'untrained' M1 may in part occur through transcallosal fibres.

The MNS seems to play a role in cross-education produced by strength training, i.e., in the transfer of motor function from an actively contracting muscle group to the contralateral homologous, relaxed muscle pair. The concurrent activation of motor areas in the two hemispheres during unilateral muscle contraction observed in cross-sectional imaging, EEG, and TMS studies [46-49] may underlie the transfer reported in chronic exercise studies. In conjunction with this activation of motor areas in the brain, in many participants there is also concurrent 'associated' activity in the muscle that is the target of cross-education but this electromyographic (EMG) activity produces trivial or no overt voluntary movement at all [49]. When participants perform unilateral practice over weeks, the task-specific performance improves in the homologous contralateral muscle because the practice repeatedly activates brain areas and the motor programs become accessible to circuits controlling the homologous muscle in the non-exercised limb [9,13,50]. After 24 sessions of maximal isometric ulnar deviation in the right arm, maximal strength increased 45% for the trained arm and 47% for the untrained arm [9]. This large cross-education effect was associated with increases in activation of the contralateral sensorimotor cortex and left temporal lobe when participants contracted their untrained left arm muscles. The left temporal lobe, especially the STS, is involved in both cross-education and the MNS, which suggests that the MNS is involved in cross-education. Because of the enlarged region of activation in the contralateral sensorimotor cortex after training, Farthing et al. [9] suggested that interhemispheric communication might be involved in the transfer of an improved motor plan, providing the untrained limb with a reference for preparation and execution of future movements. Hortobágyi et al. [13] illustrated that this modified interhemispheric communication takes the form of a decrease in interhemispheric inhibition (IHI) from the trained to the untrained left first dorsal interosseus (FDI). The corticospinal excitability in the 'untrained' (right) M1 increased, and IHI decreased by 31%. Anterior callosal regions are associated with IHI and there is evidence that the corpus callosum contributes to integration of perception and action within a subcortico-cortical network promoting a unified experience of the way the visual world and the preparation of our actions are perceived [51]. Thus, when the left temporal lobe plus the right sensorimotor cortex (i.e., due to reduced IHI) are involved in cross-education to the left arm, the MNS is most likely involved in cross-education because the MNS makes use of the very same brain areas and transcallosal connections. Functional magnetic resonance imaging (fMRI) data provide evidence for this conclusion because one-handed ulnar deviation training increased activation similarly in the respective contralateral motor strip when subjects contracted each hand in the magnet after training and there also was unique temporal lobe (mainly left middle temporal gyrus) activation after training [9].

2.1.2 Mirror training and cross-education

In mirror training the practicing hand's mirror image is superimposed over the untrained hand [19,20]. Experiments create the illusion of one limb's movements by viewing the mirror image of the other limb's actual movement. In experiments targeting the upper extremities, subjects sit at a table and place both hands inside a box with a mirror mounted on the central vertical wall separating two adjacent boxes. The mirror is aligned in the sagittal plane in front of the subject. The size of the mirror box varies between studies and can be as small as 25 by 30 cm [52] and as large as 50 by 90 cm [53]. Depending on the purpose of the study, subjects may or may not see the active hand. In the no-mirror condition the mirror is covered with a drape or opaque board. Participants keep the head in the same position under mirror and no-mirror condition to avoid any effects from the tonic neck reflex. Participants are instructed to relax and keep the hand behind the mirror in a similar orientation as the practicing hand. During motor practice, EMG is used to quantify and monitor any incidental muscle activity in the limb behind the mirror. A critical issue is to align the participant, limbs, and the mirror box so that reflection of the active limb becomes precisely superimposed upon the limb behind the mirror. In a few studies, the lower extremity was also subjected to mirror training [54,55].

Neuroanatomical, electrophysiological, and behavioural data in primates and humans thus raise the possibility that unilateral motor practice with a mirror could augment the effects of cross-education. Mirror training accelerates recovery of motor function in the affected hand after a stroke [44,56], reduces phantom pain in amputees [45,57], and improves performance of a simple skill in healthy participants' non-practiced hand [19,20,58]. The exact mechanisms are not known but there are suggestions that the MNS is involved [19,20,44,59]. Similar to unilateral strength training with the right limb, mirror training increases the corticospinal excitability of the 'ipsilateral' (right) M1 [20,58] but in this case without significant changes in IHI or short-interval intracortical inhibition (SICI) in the 'ipsilateral' (right) M1 [20]. In accordance with the simulation theory [30], these neural changes support the idea that seeing a mirror image of the exercising hand activates neurons in the 'ipsilateral' hemisphere corresponding with the motor neural network of the mirror image. The enhanced corticospinal excitability in the 'ipsilateral' M1 together with the increased activation of the 'ipsilateral' STS and the superior occipital gyrus after mirror training [19] provide a link between the MNS and mirror training. In addition to proprioceptive and cutaneous inputs, visual information via a mirror could augment cross-education of upper extremity muscle strength under the conditions of cross-education but there is currently no experimental evidence to support this prediction, possibly because this concept has not been previously considered. This review aims to fill this gap in our knowledge. Neuroanatomical, imaging, EEG, MEG, and TMS evidence suggest that the use of a mirror could augment the effects normally observed in cross-education studies. If true, the effectiveness of rehabilitation using cross-education could possibly be enhanced.

2.2 Literature search

The goal of the search was to: identify the neurobiological evidence that underlies cross-education and identify evidence to support formation of the hypothesis for augmentation of cross-education via mirror training. We performed a literature search in PubMed, CINAHL, AMED and the Cochrane Controlled trials register. For reviewing the role of the MNS in cross-education during unilateral strength training and for reviewing the role of the MNS in cross-education during mirror training the following search strategies were applied in the PubMed database and the Cochrane Controlled trials register:
#1 'mirror movement' OR 'motor overflow' OR 'interlateral transfer' OR

‘cross-limb transfer’ OR ‘intermanual transfer’ OR ‘cross-education’ OR ‘cross education’ OR ‘interlimb transfer’ OR ‘cross-transfer’ OR ‘bilateral interaction’ OR ‘strength transfer’ OR ‘bilateral facilitation’ OR ‘overflow’ OR ‘mirror activation’
#2 ‘*resistance training*’ OR ‘resistance exercise’ OR ‘power grip’ OR ‘isometric contraction’ OR ‘isometric power’ OR ‘concentric contraction’ OR ‘concentric power’ OR ‘eccentric contraction’ OR ‘eccentric power’ OR ‘voluntary contraction’ OR ‘eccentric force’ OR ‘concentric force’ OR ‘isometric force’ OR ‘muscle contraction’ OR ‘strength training’ OR ‘unilateral contraction’
#3 ‘mirror training’ OR ‘mirror therapy’ OR ‘mirror visual feedback’ OR ‘mirror-induced visual illusion’ OR ‘mirror box therapy’
#4 ‘*neuroimaging*’ OR ‘transcranial magnetic stimulation’ OR ‘*magnetoencephalography*’ OR ‘*electroencephalography*’ OR ‘*magnetic resonance imaging*’ OR ‘*positron emission tomography*’
#5 (#1 AND #2 (AND #4))
#6 (#3 AND #4)
The italicized terms are Medical Subjects Headings (MeSH) key terms. The MeSH key terms register is absent in the CINAHL and AMED database; therefore the search strategy was adapted for these two databases. The literature search specifically focused on article titles and abstracts. The search strategy applied for reviewing the role of the MNS in cross-education during unilateral strength training is labelled with #5 and the search strategy for reviewing the role of the MNS in cross-education during mirror training is labelled with #6.

The following inclusion and exclusion criteria were applied for:
A) the role of the MNS in cross-education during unilateral strength training: 1) participants had a mean age of ≤ 50 years; 2) study participants were healthy adults; 3) the exercises performed in the study were conceptually appropriate for strength improvement and were either cross-sectional, randomized or not randomized controlled trials (RCTs); 4) EMG activity in the non-exercising hand was measured during the intervention (cross-sectional studies) or cross-education was measured after completion of the intervention (RCTs), and 5) cortical activity or cortical excitability was assessed.
B) the role of the MNS in cross-education with a mirror: 1) participants had a mean age ≤ 50 years; 2) participants were healthy adults; 3) mirror training was one of the interventions, and 4) cortical activity or excitability was assessed. Studies that used bilateral muscle contractions were excluded.

Following an initial search, titles and abstracts were screened and for articles meeting the inclusion criteria, full-text articles were retrieved and examined. Furthermore, potentially relevant articles found in the reference lists of articles or those found in a private expert's database were also screened and where appropriate included for further analysis if the abstract met the inclusion criteria. Only full-text articles in English or Dutch were included. Figures 2.2 and 2.3 summarize this process for the role of the MNS in cross-education during unilateral strength training and the role of the MNS in cross-education during mirror training, respectively. Table S2.1 and S2.2 in the Electronic Supplementary Material summarize the details of the included studies.

We used the PEDro scale to assess the quality of the RCTs. This scale is based on the Delphi list [60], except for items 8 and 10 that are based on the Jadad scale [61]. The reliability of the PEDro scale is 'fair' to 'good' (intraclass correlation coefficient = .68), which makes it a good measurement for assessing the quality of RCTs [62]. One point is given for each item that meets criterion, hence a total PEDro score ranges from zero to eleven. We used a PEDro score ≥ 7 to distinguish high- vs. low-quality studies.

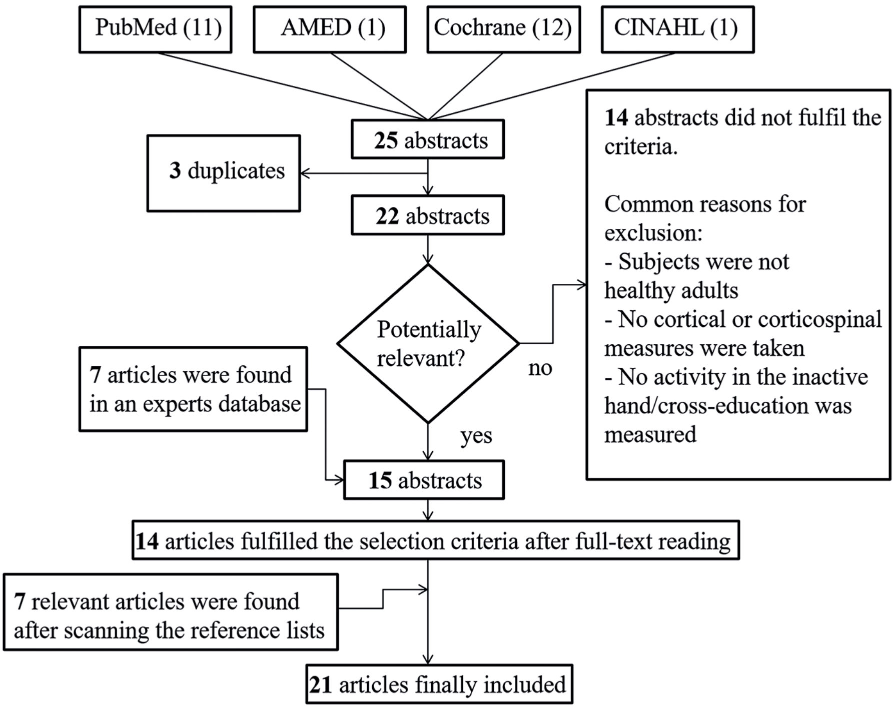

Figure 2.2 | Flow diagram and results of the literature search to address aim one of the review, concerning the role of the mirror-neuron system in cross-education during unilateral strength training.

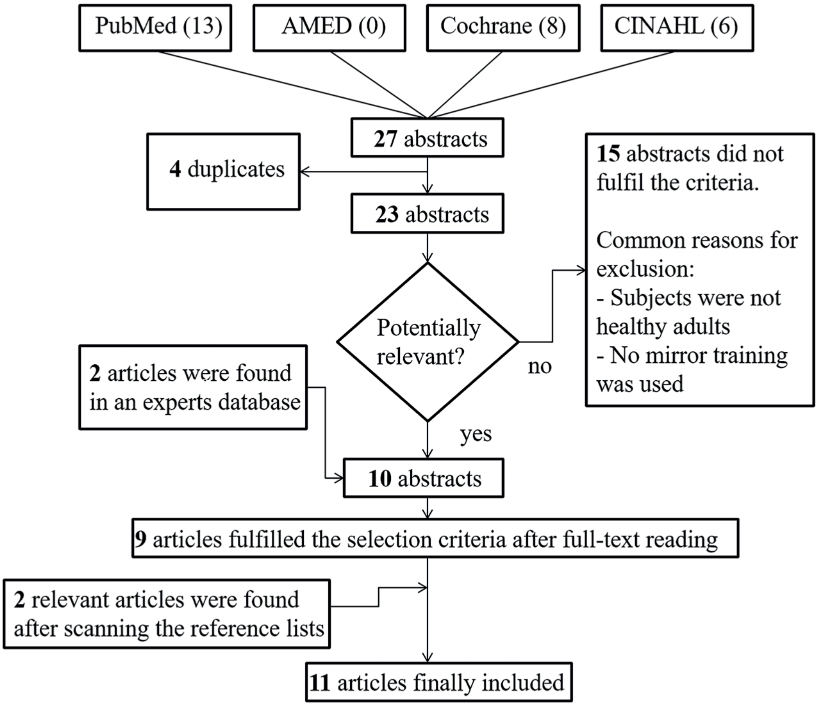

Figure 2.3 | Flow diagram and results of the literature search to address aim two of the review, concerning the role of the mirror-neuron system in cross-education during mirror training.

2.3 Results

2.3.1 Acute modulation of neural structures during unilateral muscle contraction

How unilateral muscle contractions affect cortical activation, motor cortical excitability, and corticospinal excitability can help us better understand the mechanisms of cross-education reviewed in section 3.2. One issue is the locus of control whether cortical, subcortical, and spinal structures individually or in a combination mediate cross-education and how the MNS is involved. Therefore, the lower part of Electronic Supplementary Material, Table S2.1 lists 15 cross-sectional studies that examined the changes in whole brain activity, motor cortical, and corticospinal excitability using imaging, EEG, and TMS, but it has to be noticed that none of these studies have explicitly focused on the involvement of the MNS. At the end of the section we summarize the involvement of brain structures during the execution of unimanual motor tasks that are part of the MNS. In general, participants were age 19 to 50, healthy, and right-handed young adults. The global experimental design was such that participants contracted a muscle in one hand only or contracted the right- and left-hand individually. While TMS studies shed light on the level of excitation and inhibition associated with unilateral motor activity in the two M1s, imaging and EEG studies provide clues as to which additional specific brain areas, networks, and to what extent these structures become active during unilateral contractions. Imaging studies showed that instead of activating the brain focally, unilateral muscle contractions activated a wide network of brain circuits within the active hemisphere not directly involved in controlling the contraction. In addition, unilateral contractions activated M1, supplementary motor area (SMA), and the cerebellum bilaterally so, that the activation was parametrically scaled with contraction intensity [63].

Of the imaging studies [48,63,64], Foltys et al. [64] reported specific activation of cortical areas during gentle opening and closing of the right fist ('non-involved' right cerebellum and superior temporal gyrus, and 'involved' left medial frontal gyrus), during strong left fist contraction ('non-involved', left cerebellum), and during the combination of the two tasks when the strong contraction seemed to inhibit brain activation driving gentle fist clenching of the other hand. Their TMS data also suggested the involvement of the 'non-involved' left M1 during forceful left hand contractions but the data also pointed to a role for sub-cortical and spinal networks. Compared to these data by Foltys et al. [64], Newton et al. [48] reported somewhat more widespread and bilateral activation of the lateral premotor area, M1, and SMA during unilateral wrist extension. Bilateral activation of the latter two structures suggests an overlap with elements of the MNS because performing similar motor tasks in a mirror and performing unimanual motor tasks both activate these structures. Sehm et al. [63] had 15 healthy volunteers performing right isometric wrist flexion at 10%, 20%, 30%, and 70% of maximal isometric force. During scanning, EMG activity was recorded bilaterally from flexor carpi radialis (FCR), extensor carpi radialis (ECR), biceps brachii (BB), and triceps brachii (TB). Mirror EMG activity was observed in left FCR during 20%, 30%, and 70% of force. In contrast to Foltys et al. [64], who reported much less widespread activation during a strong grip probably due to the use of different magnetic resonance sequences, increasing force was associated with a linear and bilateral increase in activation of the M1s, SMA, caudal cingulate, and cerebellum, with the first two of these structures being also part of the MNS. The mirror EMG activity in the left FCR during the contractions on the right side correlated with activity in bilateral M1, SMA, and the cerebellum. These data suggest that the activated regions might reflect sensorimotor processes underlying and perhaps controlling mirror EMG activity in the 'resting' left hand. EEG data showed that prior to unilateral contractions precentral regions in the 'involved' (left) vs. 'non-involved' (right) hemisphere were more active and that the contractions also bilaterally activated parietal cortices [47], an observation in line with the chronic changes observed by Farthing et al. [18] using imaging.

Unlike fMRI studies, TMS studies focused on the magnitude and nature of activation in the 'non-involved' or ipsilateral motor brain areas; in particular that of M1, during unilateral muscle contraction. Several studies, confirming the imaging data, reported that the 'non-involved' M1 actually becomes active and its excitability parametrically increases with the intensity of unilateral muscle contraction regardless whether participants contracted a small finger muscle or the larger wrist flexors [13,49,64-67]. In addition to changes in corticospinal excitability, when healthy volunteers abducted the right little finger, there was a decrease in short-interval intracortical inhibition, SICI, in the 'non-involved' (right) M1. There was also a significant increase in F-wave amplitude, a measure of spinal excitability, in the resting, left, little finger abductor muscle, suggesting the involvement of both motor cortical and segmental paths [65].

Not only did a unilateral muscle contraction decrease SICI but it also lessened the IHI from the involved to the non-involved M1 [67], an effect that was also observed in a chronic exercise study and magnified by the end of 20 sessions of strength training [13]. Further, IHI and SICI were inversely correlated, meaning that in the presence of more IHI, there was a significant extra decrease in SICI. This inverse correlation suggests that intracortical inhibition brought about by unilateral muscle contraction modulates interhemispheric inhibition, especially during high intensity (70% maximal voluntary contraction [MVC]) voluntary contractions [67]. Another form of motor cortical interhemispheric inhibition is the ipsilateral silent period (iSP) that presumably tests gamma-aminobutyric acid (GABA)-B neurons compared with IHI that tests GABA-A [68]. The onset latency of the iSP, measured in the mildly contracting left hand while the right hand was strongly contracted, was prolonged ~17 ms, suggesting that IHI probably delayed or suppressed overflow from the left to right M1 [66]. These consistent observations in TMS studies are complicated by the finding of a unique form of strong inhibition of the H-reflex in the relaxed right FCR during contraction of the left wrist flexors [69]. Because these effects were present without changes in motor evoked potentials (MEPs) produced by brainstem stimulation, the authors suspected that presynaptic inhibition caused the H-reflex depression. A recent chronic training study has shown subtle bilateral changes in H-reflex recruitment curve after unilateral strength training but it is unclear if the changes in measures of the H-reflex correlated with the magnitude of cross-education [70].

While in most of these experiments [67,69,71,72] participants kept muscle activity in the non-contracting limb minimal, such ‘associated’ activity is normally present during unilateral muscle contraction [49]. The source of this muscle activity probably lies in the ‘non-involved’ M1 [49]. When healthy volunteers strongly contracted the right elbow flexors, muscle activation also appeared in the ‘resting’, left elbow flexors. This unintentional (associated or mirror) activity of the left elbow flexors increased the size of MEPs more than voluntary contractions of the left biceps performed with matched levels of background EMG. The silent period was equally long in associated and voluntary contractions. The authors concluded less of a role for interhemispheric processes and an obligatory role for the right hemisphere so that the source of the associated or mirror activity is the concurrent activation of the two hemispheres, a conclusion confirmed by a model described in a recent analysis [73]. These results seem somewhat in contrast to the conclusions derived from other studies that measured IHI and its modulation by unilateral muscle contractions, suggesting the involvement of GABA-A transcallosal neurons tested by IHI [13,67,74]. These contradicting results make it difficult whether IHI or bilateral cortical activation is the mechanism that may engage the MNS. Chronic unilateral strength exercise studies with and without a mirror should provide evidence which of the two mechanisms engages the MNS in cross-education.

Forming a bridge between these exploratory acute studies and the chronic exercise studies are two studies that used short-term interventions albeit ballistic movements and not strength training. Lee et al. [72] examined cross-education related changes in corticospinal excitability during one session of unilateral motor practice. Three hundred trials of rapid right index finger abductions increased the peak acceleration of the non-practiced left index finger by 62%. The motor practice also increased the size of MEPs in the non-practiced left index finger abductors. To probe the mechanism of cross-education, low frequency, repetitive TMS (rTMS) of the ‘practiced’ (left) M1 inhibited motor learning as peak acceleration decreased 13% and corticospinal excitability indexed with MEP size decreased 28% in the right index finger. rTMS of the ‘non-practiced’ (right) M1 decreased only peak acceleration of the left index finger 16%. Sham rTMS had no effect. Participants were instructed to avoid ‘associated’ activity or ‘mirroring’ in the non-practicing resting left hand, and there was still a large amount of cross-education after unilateral practice of a ballistic finger task as was also the case after chronic practice with low-skill isometric finger muscle contractions [13]. As discussed in detail, it is not clear if the magnitude of cross-education is greater with or without the presence of associated or mirror activity. Although participants volitionally suppressed the associated activity (EMG activity in the resting right quadriceps muscle < 50 μV), there was still the expected amount of cross-education [13]. Whereas in another study there was documented associated activity of 10-20% of MVC during unilateral strength training also producing somewhat larger amount of cross-education [75], suggesting low if any association between cross-education and associated activity.

In this respect Bologna et al. [71] reported that the transfer was independent of associated (mirroring) activity because transfer occurred even with a tendency for mirroring to decline. The transfer also occurred without changes in IHI but the basal level of IHI at the start of the training affected how much mirroring would change. Mirroring per se does not seem to be critical in transfer, a suggestion also made previously [13]. Baseline IHI determines how well participants can learn to focus their motor commands on the training task and minimize overflow to the opposite hemisphere [71]. There was associated activity present in the right index finger abductor [76] and right little finger abductor [77] even after inhibitory rTMS of the right dPMC, an area involved in motor planning. Modulation of cortical excitability of specific brain areas with real and sham rTMS produced no changes in the associated activity [76,77].

These cross-sectional exploratory and short-term training studies collectively suggest that associated or mirror activity is the result of concurrent activation of the two hemispheres during unilateral movements and neither interferes with nor augments the magnitude of cross-education. While it is unclear if IHI is related to this concurrent activation in cross-education studies, a chronic intervention study seems to suggest that reduction in IHI is a mediator of cross-education [13]. In addition, a cross-sectional study shows that the initial level of IHI may also affect the magnitude of cross-education [71]. Data from these studies [48,63,64] suggest that many elements of the MNS became activated during the execution of unimanual motor tasks and these elements include M1 [48,63], SMA [48,63], medial frontal gyrus [64], and the lateral premotor area [48].

2.3.2 Cross-education and neural adaptations after chronic unilateral strength training

Because neural adaptations mediate cross-education, here we review studies designed to produce cross-education and explored the potential role for M1 and other brain structures. We note that none of these studies have explicitly examined the role of the MNS in cross-education. Imaging [9,18] and TMS [13,50,78,79] were the two main approaches to quantify neural adaptations in healthy adults subjected to chronic unilateral strength exercise interventions. The general design of these studies included right-handed healthy adults in a pre-post intervention model. Strength training targeted the dominant right hand with the left hand kept at rest [9,13,50,78]. In addition, the left hand was immobilized in a cast or sling [18,79]. The control groups did not exercise or performed imagery of strength training [9].

Despite the differences in intervention duration (range: 3 to 8 weeks) and number of training sessions (range: 9 to 24 sessions) between these studies, each study reported a significant cross-education effect and cortical or corticospinal adaptations. Maximal voluntary strength of the left wrist [9,50], index finger [13] and BB [78] increased 47% [9], 9% [50], 28% [13], and 19% [78], respectively. In addition, cross-education prevented strength loss in the left immobilized wrist [18] and elbow flexors [79] in contrast to the 11% decrease in left wrist and 20% decrease in left elbow flexor strength in the control group.

So far no studies have examined the dose-response relationship with respect to cross-education. Zhou [11] reported no obvious relationship between the intensity (i.e., the amount of strength per exercise expressed in % MVC) and duration of training (i.e., the period of training in weeks) and the magnitude of cross-education. Figure 2.4 depicts the relationship between the quantity of practice and the increase in strength of the right, trained and the left, untrained arm based on data extracted from six chronic cross-education studies. Although the experimental context differed between the six studies, the association between the amount of practice and the increase in strength in the right trained hand ($r = 0.69$) and left untrained hand ($r = 0.75$) are reasonably strong, with the regression slopes nearly identical. The data suggest that performance gains in the trained limb and the magnitude of transfer to the untrained limb are associated with the quantity of practice.

In these six studies there were significant increases in cortical activity or corticospinal excitability after unilateral strength training, whereas the control groups showed small and non-significant changes. Imaging studies showed new cortical activation after training associated with the untrained arm resembled the areas involved in motor learning [9]. There was especially strong adaptation in the sensorimotor cortex for

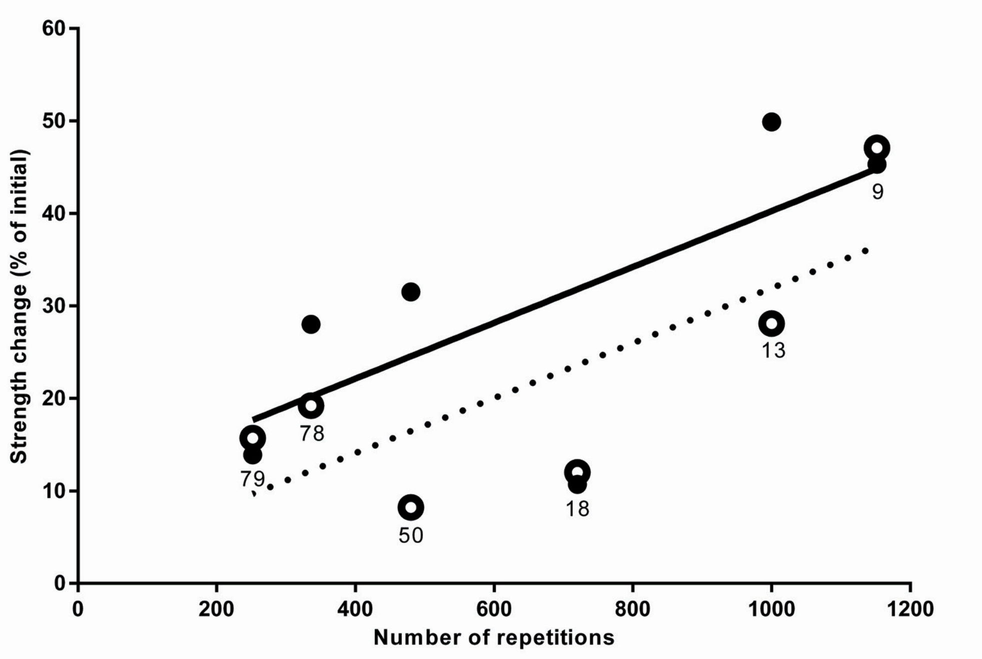

Figure 2.4 | Strength gains in the trained right and untrained left upper extremity muscles in relation to motor practice. Vertically oriented data pairs come from specific studies, denoted by the reference number. *Closed* and *open symbols*, respectively, denote trained and untrained arm. The *solid* and *dashed line*, respectively denote the linear relationship for the trained right arm ($R^2 = 0.48$; $y = 0.0302x + 10.056$) and untrained left arm ($R^2 = 0.57$; $y = 0.0297x + 2.1865$).

the untrained arm after training. Further, the bilateral increase in activation in M1 suggests a potential role of interhemispheric plasticity [9], underscored by the increases in activation of the premotor and visual cortices in the follow-up study [18].

Recent TMS studies provide some confirmatory evidence for the concept of interhemispheric plasticity. Unilateral right index finger training significantly increased corticospinal excitability in the 'untrained' (right) M1 and significantly decreased IHI from the 'trained' (left) to the 'untrained' (right) hemisphere during contractions of the trained right FDI [13]. Wrist extension strength training also improved cortical voluntary activation in the untrained muscles exhibiting 8% cross-education [50]. Unlike this latter study that reported non-significant changes in corticospinal excitability [50], Kidgell et al. [78] reported ~30% significant increase in MEP amplitude in the left, untrained BB. Immobilization of the non-dominant elbow reduced elbow flexor muscle strength 11 N but immobilization coupled with strength training of the dominant arm's elbow flexors protected against strength loss in the immobilized limb and increased its strength by 5 N [79]. Because corticospinal excitability in the pathways projecting to the untrained, immobilized limb after training did not decrease, the training through some other neural mechanism helped retain muscle size and strength [79].

The mechanism is still unknown as to how the changes in excitability of the putative neural structures allow volunteers to exert more force by the untrained muscles because, unlike in a previous study [13], these authors did not examine the relationship between the changes in excitability and changes in muscle force (i.e., cross-education). Although these chronic studies did not examine the involvement of the MNS in cross-education, their results suggest a role of this system in evoking cross-education. The significant enlarged regions of activation found after completion of the training program in the ‘untrained’ (right) sensorimotor cortex and M1, and the ‘trained’ (left) temporal lobe, premotor cortices and visual cortices [9,18] during muscle contractions of the left untrained hand, suggest the involvement of cortical structures associated with the MNS.

2.3.3 Acute and chronic modulation of neural structures by mirror training

Electronic Supplementary Material, Table S2.2 presents 11 studies that assessed cross-education related changes in cortical activity, motor cortical excitability or corticospinal excitability during mirror training. The participants’ were aged between 19 and 50 and except for two participants, were all right-handed. Fukumura et al. [80] did not report participants’ handedness. The complexity of the executed movements in the mirror box differs between studies. Three studies used complex hand movements [20,23,81]; three studies used simple wrist flexion and extension movements [53,80,82]; one study used simple finger tapping movements [19]; the study of Shinoura et al. [83] used repetitive hand clenching; one study used finger thumb opposition movements [58], and Tominaga et al. [52,84] used a simple pencil holding task. Neural adaptations produced by chronic or acute mirror training were assessed with TMS (six studies), MEG (two studies) or fMRI (three studies). Additionally, Nojima et al. [20] used continuous theta burst stimulation (cTBS) of the ‘untrained’ (right) M1 or (right) occipital area in an attempt to abolish the effects caused by mirror training. The changes in motor cortical inhibition following mirror training were assessed by SICI and IHI [20,23] or the iSP [53].

The data from three studies illustrate that different brain areas contribute to the increased task performance of the untrained left hand after chronic [23,81] and acute [20] mirror training. The two chronic studies found after four days of fine motor task mirror training that hand dexterity of the untrained left hand increased significantly 12% [81] and 20% [23] more compared with the control group performing the standard cross-education intervention program. This increased left hand dexterity was accompanied by an increase in brain activity of the 'ipsilateral' (right) dPMC, and 'contralateral' (left) inferior parietal lobe, ventral premotor cortex (vPMC), and supplementary motor cortex [81] and by an increase of SICI in the 'contralateral' (left) M1 [23]. Thereby, Läppchen et al. [23] observed a significant decrement of SICI in the 'ipsilateral' (right) M1 following mirror training and a significant increase of intracortical facilitation (ICF) in the 'contralateral' (left) M1 in the control group. The acute study of Nojima et al. [20] found an increase in left hand dexterity after ten sessions of right hand exercise in the mirror box without changes in IHI and SICI. An increase in untrained left hand dexterity was absent when the exercising right hand was viewed without a mirror and was smaller after cTBS of the 'untrained' (right) M1.

Four studies investigated if the EMG activity together with corticospinal excitability of the non-exercising hand was involved in acute mirror training [53,58,80,82]. Garry et al. [58] found that the increased MEPs in the non-exercising FDI showed a trend toward significance when a mirror reflection of the active hand performing finger-thumb opposition movements was viewed compared with viewing the active hand directly. Carson and Ruddy [53] observed the same, but significant, effects during left wrist flexion movements and additionally they found that the EMG activity during the iSP was significantly more suppressed for the vision condition compared with the mirror condition at movement onset. In contrast, Funase et al. [82] found little difference in MEPs of the non-exercising right FDI and FCR muscles between viewing the active left hand directly and viewing a mirror reflection of the active left hand. The somatosensory evoked potentials, recorded from the 'ipsilateral' (left) somatosensory cortex, were not significantly different between tasks. In agreement with Garry et al. [58], Fukumura et al. [80] found that MEPs in the non-exercising hand were significantly increased when viewing a mirror reflection of the active hand compared with viewing a marked position between both hands.

Four studies investigated, which brain areas were active during mirror training [19,52,83,84]. Shinoura et al. [83] found that viewing a mirror reflection of repetitive right hand clenching caused unique bilateral activation of the occipital lobe, the 'contralateral' (left) cerebellum and the 'ipsilateral' (right) M1 compared with the eyes closed condition. Likewise, Tominaga et al. [52] found significant increases in activity of the ‘ipsilateral’ (right) M1 controlling the non-exercising hand when viewing a mirror reflection of the active right hand holding a pencil. This increased activity was not present when participants directly viewed the right hand. Furthermore, the ‘contralateral’ (left) M1 was significantly more active when viewing a mirror reflection of the left hand holding a pencil than when viewing the left hand during the same task [52,84]. Additionally, Matthys et al. [19] reported that the ‘contralateral’ (right) superior temporal and occipital gyrii were significantly more active during mirror training with the left hand compared with directly viewing finger tapping movements of the right hand.

2.3.4 A model for cross-education of maximal voluntary strength

The 21 reviewed studies illustrate that unilateral strength training produces cross-education and also changes in multiple cortical areas, including the areas that form the core of the MNS. Unilateral strength exercises performed in cross-sectional studies also activated similar brain areas that showed adaptations after the interventions. To illustrate, the ipsilateral M1 [47,48,63,72], premotor cortex [48], SMA [48,63], cerebellar lobe [63,64] and primary somatosensory cortex [47] were active during unilateral strength exercises with the right hand and were also involved in the chronic cross-education effects appearing in the untrained left hand [9,13,18,50,78,79]. This commonality in activation would suggest that the brain areas active during one and multiple sessions of strength exercises contribute to the chronic cortical effects observed after cross-education. In other words, unilateral muscle contractions activate brain areas and these same areas also exhibit adaptations after multiple sessions and involve elements of the MNS. Table 2.1 provides an overview of the brain areas involved in acute and chronic motor practice with the dominant right hand and highlights the elements of the MNS that the training also activated.

However, the picture of how intrahemispheric and interhemispheric activation during unilateral muscle contraction contributes to cross-education of strength is not consistent and differs between chronic and acute studies. The SICI in the ‘non-involved’ (right) M1 of the exercising hand decreased significantly during contractions of right hand muscles [13,65,67] but Hortobágyi et al. [13] found no decrease in SICI of the ‘untrained’ (right) M1 after multiple strength training sessions of the right FDI. This suggests that SICI in the ‘non-involved’ (right) M1 contributes to the mirror activity observed during the acute execution of unilateral strength exercises but does not contribute to the cross-education of strength after chronic training; perhaps under these conditions the circuits involved in SICI are less adaptable. The observed

Table 2.1 | Brain activation, including elements of the MNS, by unilateral strength-training and strength exercises with the dominant right arm

Study[a]	Intervention/ motor task	Activated elements of the MNS in the LH during acute and after chronic unilateral motor practice with the dominant right arm	Activated elements of the MNS in the RH during acute and after chronic unilateral motor practice with the dominant right arm	Brain areas activated in the LH during acute and after chronic unilateral motor practice with the dominant right arm	Brain areas activated in the RH during acute and after chronic unilateral motor practice with the dominant right arm
Farthing et al. [9]	Chronic training of isometric ulnar deviations	Ventral M1 Inferior temporal gyrus Medial occipital gyrus	M1 Medial occipital gyrus	Ventral M1 Ventral somatosensory cortex Anterior middle temporal gyrus Posterior middle temporal gyrus Inferior temporal gyrus Medial occipital gyrus Posterior medial cerebellum Lateral cerebellum	M1 Primary somatosensory cortex Medial occipital gyrus Posterior medial cerebellum
Farthing et al. [18]	Chronic training of isometric handgrip contractions	Premotor cortex Medial occipital gyrus	M1	Premotor cortex Medial occipital gyrus	M1
Hortobágyi et al. [13][b]	Chronic training of isometric first dorsal interosseus contractions		M1		M1

Table 2.1 | *(Continued)*

Study[a]	**Intervention/ motor task**	**Activated elements of the MNS in the LH during acute and after chronic unilateral motor practice with the dominant right arm**	**Activated elements of the MNS in the RH during acute and after chronic unilateral motor practice with the dominant right arm**	**Brain areas activated in the LH during acute and after chronic unilateral motor practice with the dominant right arm**	**Brain areas activated in the RH during acute and after chronic unilateral motor practice with the dominant right arm**
Lee et al. [50]	Chronic training of isometric wrist contractions	Not tested	M1	Not tested	M1
Kidgell et al. [78]	Chronic training of isokinetic elbow flexor movements	M1	M1	M1	M1
Pearce et al. [79]	Chronic training of isokinetic elbow flexor movements	M1	M1	M1	M1
Newton et al. [48]	Acute bouts of isometric wrist extensions	SMA M1 Lateral premotor area	SMA M1 Lateral premotor area	SMA M1 Lateral premotor area	SMA M1 Lateral premotor area
Muellbacher et al. [65][c]	Acute bouts of abductor pollicis brevis contractions	Not tested	M1	Not tested	M1

Table 2.1 | *(Continued)*

Study[a]	Intervention/ motor task	Activated elements of the MNS in the LH during acute and after chronic unilateral motor practice with the dominant right arm	Activated elements of the MNS in the RH during acute and after chronic unilateral motor practice with the dominant right arm	Brain areas activated in the LH during acute and after chronic unilateral motor practice with the dominant right arm	Brain areas activated in the RH during acute and after chronic unilateral motor practice with the dominant right arm
Foltys et al. [64]	Acute bouts of repetitive hand clenching	Medial frontal gyrus M1		Medial frontal gyrus M1	Superior temporal gyrus Anterior cerebellar lobe
Hoy et al. [66]	Acute bouts of abductor digiti minimi contractions	M1	M1	M1	M1
Sehm et al. [63]	Acute bouts of isometric wrist contractions	SMA M1	SMA M1	SMA M1 Caudal cingulate cortex Cerebellum [lobule IV]	SMA M1 Caudal cingulate cortex Cerebellum [lobule IV-V]
Perez and Cohen [67][d]	Acute bouts of isometric wrist contractions	Not tested	M1	Not tested	M1
Lee et al. [72]	Acute bouts of ballistic index finger movements	M1	M1	M1	M1
Cramer et al. [46]	Acute bouts of index finger tapping	Precentral gyrus	Precentral gyrus	Precentral gyrus	Precentral gyrus

Table 2.1 | *(Continued)*

Study[a]	**Intervention/ motor task**	**Activated elements of the MNS in the LH during acute and after chronic unilateral motor practice with the dominant right arm**	**Activated elements of the MNS in the RH during acute and after chronic unilateral motor practice with the dominant right arm**	**Brain areas activated in the LH during acute and after chronic unilateral motor practice with the dominant right arm**	**Brain areas activated in the RH during acute and after chronic unilateral motor practice with the dominant right arm**
Hübers et al. [74][e]	Acute bouts of fast index finger abductions	Not tested	Not tested	Not tested	Not tested
Bologna et al. [71][e]	Acute bouts of ballistic index finger movements	M1	Not tested	M1	Not tested
Zijdewind et al. [49]	Acute bouts of isometric elbow flexor contractions	M1	M1	M1	M1

LH = left hemisphere; MNS = mirror-neuron system; M1 = primary motor cortex; RH = right hemisphere; SMA = supplementary motor area

[a] In these studies, unilateral contractions were performed with right hand or arm muscles while the left hand and arm were at rest

[b] Interhemispheric inhibition from the 'trained' (left) to the 'untrained' (right) M1 was significantly reduced following the strength training program

[c] Short-interval intracortical inhibition was significantly reduces in the 'non-involved' (right) M1 during contractions

[d] Short-interval intracortical inhibition was significantly reduced in the 'non-involved' (right) M1 + interhemispheric inhibition from the 'involved' (left) to the 'non-involved' (right) M1 was significantly reduced during contractions

[e] Significantly inverse correlation between changes in interhemispheric inhibition from the 'involved' (left) to the 'non-involved' (right) M1 and electromyographic activity in the resting left hand

contradiction of SICI in acute vs. chronic exercise training may also have something to do with the level of contraction force (i.e., 80% MVC [13] vs. 10%, 30%, and 70% MVC [67]) and the type of contractions (i.e., isometric contractions [13] vs. shortening contractions [65]), because SICI in the 'non-involved' (right) M1 is diminished with increasing contraction intensity and is further diminished during forceful lengthening compared with shortening contractions [15]. IHI from the 'involved' (left) to the 'non-involved' (right) M1 decreased acutely during isometric contractions of the right wrist [67] and also decreased chronically, with a decrease in magnitude of IHI over an increasing number of unilateral strength training sessions [13]. In contrast, Kidgell et al. [78] found no changes in duration of the iSP in either BB muscles, suggesting that there were no changes in this form of interhemispheric inhibition after chronic unilateral strength training. A possible explanation for this observed contrast is the difference between the two cortical inhibitory circuits, suggesting a more prominent involvement of the circuits mediating IHI than iSP in cross-education. After disruption of the right dPMC, there was an increase in mirror movements during isometric contractions of the left hand [76,77], which suggests an increase in magnitude of IHI between the right and left dPMC when disruption of the right dPMC is absent.

This suggestion is reinforced in both studies by the absence of mirror movements when the right dPMC was not disrupted. Hoy et al.,[66] reported in addition to the absence of mirror activity, a significant later ipsilateral than contralateral silent period in the contracting abductor digiti minimi muscle, which indicates that mirror activity is probably suppressed via IHI. Because a decreased IHI contributes to mirror activity and cross-education was only observed with dominant right hand training there is a suggestion that the cross-education of strength is much greater when the dominant hand is trained in right-handed individuals [85].

Cross-education produced by chronic strength training of the right arm was accompanied by significant increases in activation of the 'trained' (left) inferior and middle temporal gyrii and the medial occipital cortex [9,18] but such activation pattern did not appear in scans acquired in cross-sectional studies. The left temporal lobe is involved in both cross-education and the MNS, which implies that the MNS may have a role in cross-education through direct observation of the practicing limb or the cross-educated limb. The enlarged activation regions in the 'trained' brain's frontoparietal areas and the reduction in IHI following training indicate the importance of interhemispheric communication from the trained to the untrained brain. Interhemispheric communication from the trained to the untrained hemisphere may result in an improved motor plan that can provide the untrained limb with a reference for preparation and execution of future movements. Figure 2.5 combines a model of cross-education and the MNS [3,8] based on the reviewed literature and previously reported models of cross-education [14,85].

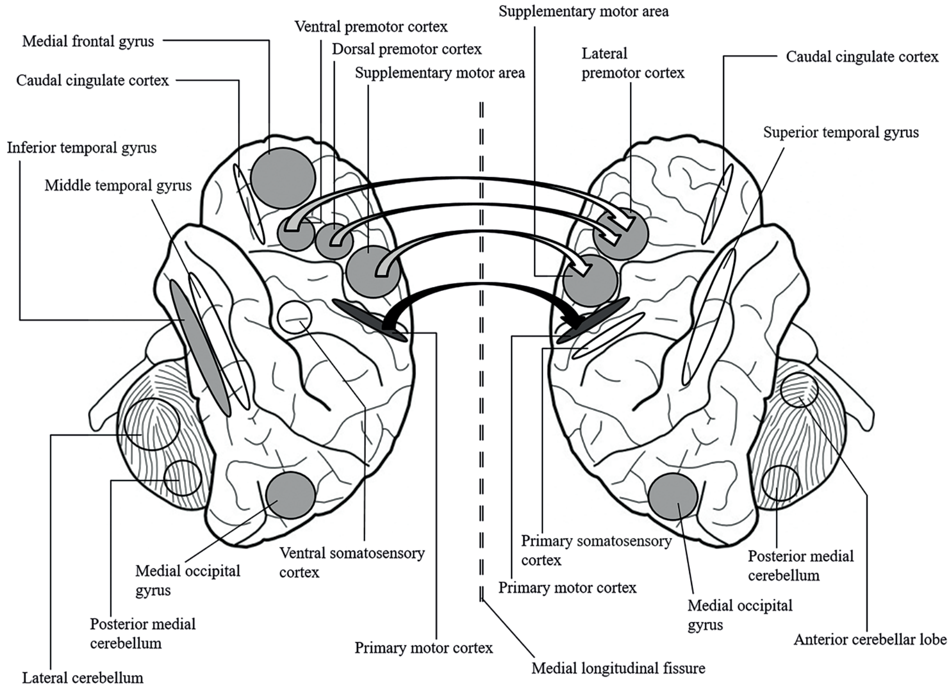

Figure 2.5 | A conceptual model of cross-education of strength produced by unilateral contractions of a right upper extremity muscle, incorporating previous models of the mirror-neuron system [3,8] and cross-education [14,85]. The model identifies the brain areas that interconnect the two hemispheres and play a hypothetical (*unfilled white arrows*) or experimentally verified role (*filled black arrows*) in cross-education of muscle strength from the trained right to the untrained left limb. The map is displayed as left hemisphere on the left and right hemisphere on the right. *Shaded areas* denote the regions of the brain involved in the mirror-neuron system and in mediating cross-education; *darker shading* means more definitive evidence. Evidence for the involvement of structures in the left hemisphere: medial frontal gyrus [64]; caudal cingulate cortex [48,63]; supplementary motor area [48,63]; dorsal premotor cortex [18,48]; ventral premotor cortex [18,48]; primary motor cortex [9,46,48,49,63,64,66,71,72,78,79]; ventral somatosensory cortex [9]; middle temporal gyrus [9]; inferior temporal gyrus [9]; lateral cerebellum [9,63]; posterior medial cerebellum [9,63]; medial occipital gyrus [9,18]. Evidence for the involvement of structures in the right hemisphere: caudal cingulate cortex [63]; supplementary motor area [48,63]; lateral premotor cortex [48]; primary motor cortex [9,13,18,46,48-50,63,65-67,72,78,79]; primary somatosensory cortex [9]; superior temporal gyrus [64]; anterior cerebellar lobe [63,64]; posterior medial cerebellum [9,63]; medial occipital gyrus [9].

The MNS consists of a forward and inverse model. The inverse model begins with the processing of visual information in the inferior and middle temporal gyrus, which provides a higher-order visual description of the observed action. This description is then transmitted from the temporal lobe, via the superior parietal lobe, to the frontal lobe where the goal of the action and the specific motor program for achieving that action is coded via the dPMC, vPMC, and SMA. The forward model transmits the efference copy of the motor plan back from the premotor cortices, via the superior parietal lobe, to the temporal lobe, where the predicted sensory consequences of the planned imitative action are compared with the visual description of the observed action. Evidence for involvement of the superior parietal lobe in cross-education is lacking, which suggests that beside the MNS, other circuits are important for evoking cross-education. As suggested in the beginning of this section, interhemispheric effects are likely to affect these circuits. The model of Carroll et al. [14] suggests that interhemispheric connections between different brain structures play an important role in cross-education of muscle strength. However, only two TMS studies showed a reduction in IHI from left, 'involved' to the 'non-involved', right M1 during isometric contractions of the right hand [13,67]. By extension from two other TMS studies not directly examining cross-education effects, the implication is that the interhemispheric connections between right and left dPMC might also contribute to cross-education [76,77]. fMRI and TMS studies found that M1, primary somatosensory cortex (S1), premotor cortex, caudal cingulate cortex, and SMA were active in both hemispheres during isometric contractions of the right hand, suggesting that the activation is concurrent, mediated by interhemispheric overflow or both. Although interhemispheric plasticity has been suggested as a mechanism of cross-education [13,14], it is unclear in which elements of and at what stage of processing in the MNS such a transfer would occur. When the goal of the action and the specific motor program for achieving that action is transferred from the left frontoparietal mirror system via transcallosal connections to the right frontoparietal mirror system, imaging would detect bilateral activation in M1 during unilateral strength training. Two fMRI studies observed bilateral M1 activity during isometric strength exercises with the right hand [48,66] and six studies found enlarged activation in [9,18] or increased corticospinal excitability of [13,50,78,79] the 'untrained' (right) M1 after multiple sessions of strength exercises together with a significant increase in strength of the untrained left hand. These results support the aforementioned cortical mechanism but more research examining the transcallosal connections mediating cross-education is needed for development of a definitive cross-education model.

2.3.5 Integration: the mirror-neuron system and cross-education after mirror training

Table 2.2 provides an overview of the brain areas including the elements of the MNS, which contribute to mirror training when healthy adults train a right upper extremity muscle. Based on the reviewed literature, Figure 2.6 shows a model of how the MNS contributes to mirror training when healthy adults train a right upper extremity muscle. The reviewed studies support the evidence that the MNS is involved in mirror training but whether this system is also involved in cross-education is presently unknown and forms the very hypothesis of the present review.

Two studies did examine the cross-education related cortical adaptations after multiple sessions of mirror training but these studies used only four sessions of mirror training [23,81]. The brain areas involved in mirror training with the right hand were the 'ipsilateral' (right) M1 [20,52,53,58,83], SMA [83], occipital lobe [83] and cerebellum [83] and the 'contralateral' (left) superior temporal sulcus [19], superior occipital gyrus [19] and M1 [52,58,83,84]. Brain areas that became additionally active after four sessions of mirror training were the 'contralateral' (left) inferior parietal lobe and vPMC and the 'ipsilateral' (right) dPMC [81]. The activity in the superior temporal sulcus, occipital cortex, inferior parietal lobe and the premotor areas strengthen the possibility that the MNS is involved in mirror training. However, only one study observed bilateral activation in the M1 during mirror training, requiring further research to firmly conclude that the MNS contributes to cross-education. Nojima et al. [20] reported no changes in IHI or SICI in the 'ipsilateral' (right) M1 during mirror training with the right hand, an observation that is inconsistent with the idea that the same transcallosal mechanisms are active during unilateral strength training with and without a mirror. In addition, Läppchen et al. [23] found after four days of right-handed unilateral skill training a significant increase in SICI in the 'contralateral' (left) M1 for the mirror training vs. the control group, but no changes in magnitude for ICF and IHI were observed. For the mirror training group only, the increased magnitude of SICI in the 'contralateral' (left) M1 was accompanied by a significant decrease of SICI in the 'ipsilateral' (right) M1 and a significant increase in the untrained left hand dexterity, which suggest a role for SICI in evoking cross-education effects with mirror training. These data suggest that the active, left M1 (ipsilateral to the hand behind the mirror) plays a role in cross-education with a mirror and probably this effect is not mediated by IHI. The data point to the possibility that if participants practice the same skill with or without a mirror, different networks may cause the adaptations in the trained brain and the untrained brain [23]. Future studies will have to confirm

Table 2.2 | Brain activation, including elements of the MNS, by unilateral motor practice with the dominant right hand while viewing a mirror image of the active limb

Study[a]	Intervention/ motor task	Activated elements of the MNS in the LH during acute and after chronic unilateral motor practice with the dominant right arm	Activated elements of the MNS in the RH during acute and after chronic unilateral motor practice with the dominant right arm	Brain areas activated in the LH during acute and after chronic unilateral motor practice with the dominant right arm	Brain areas activated in the RH during acute and after chronic unilateral motor practice with the dominant right arm
Hamzei et al. [81]	Chronic training of complex hand movements	Ventral PMC SMA	Dorsal PMC	Inferior parietal lobe Ventral PMC SMA	Dorsal PMC
Läppchen et al. [23][b,c,d]	Chronic training of complex hand movements	Not tested	Not tested	Not tested	Not tested
Nojima et al. [20]	Acute bouts of complex hand movements	Not tested	M1	Not tested	M1
Garry et al. [58]	Acute bouts of thumb opposition movements	Not tested	M1	Not tested	M1
Shinoura et al. [83]	Acute bouts of repetitive hand clenching	SMA M1 Occipital cortex	M1 Occipital cortex	SMA M1 Occipital cortex Cerebellum (outside)	M1 Occipital cortex

Table 2.2 | *(Continued)*

Study[a]	Intervention/ motor task	Activated elements of the MNS in the LH during acute and after chronic unilateral motor practice with the dominant right arm	Activated elements of the MNS in the RH during acute and after chronic unilateral motor practice with the dominant right arm	Brain areas activated in the LH during acute and after chronic unilateral motor practice with the dominant right arm	Brain areas activated in the RH during acute and after chronic unilateral motor practice with the dominant right arm
Tominaga et al. [84]	Acute bouts of a pencil holding task	M1	Not tested	M1	Not tested
Tominaga et al. [52]	Acute bouts of a pencil holding task	M1	M1	M1	M1
Matthys et al. [19]	Acute bouts of simple finger tapping movements	Superior parietal lobe M1 PMC Middle occipital gyrus	Superior temporal sulcus superior occipital gyrus	Superior parietal lobe M1 PMC Middle occipital gyrus Somatosensory cortex	Superior temporal sulcus superior occipital gyrus Middle temporal gyrus Cerebellum [vermis 4/5/6]

LH = left hemisphere; MNS = mirror-neuron system; M1 = primary motor cortex; PMC = premotor cortex; RH = right hemisphere; SMA = supplementary motor area

[a] In these studies participants performed unilateral exercises with the right hand while the left hand was at rest

[b] Short-interval intracortical inhibition increased significantly in the ‘contralateral’ (left) M1 following mirror training compared with the control group

[c] Intracortical facilitation in the left M1 increased significantly following training for the control group only

[d] Mirror training significantly reduced the magnitude of short-interval intracortical inhibition in the ‘ipsilateral’ (right) M1

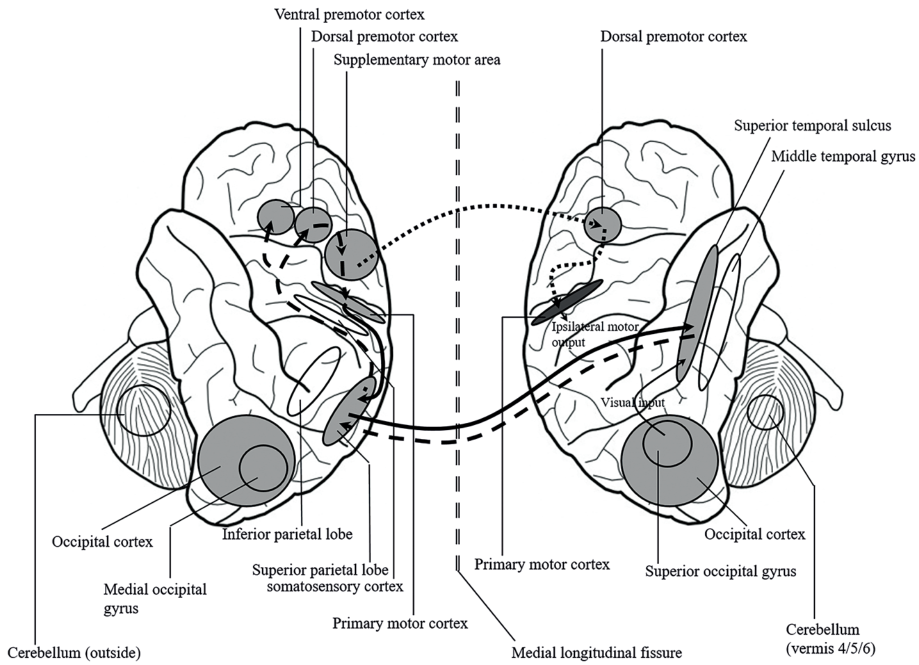

Figure 2.6 | A conceptual model of how the mirror-neuron system mediates cross-education from the right to the left limb produced by motor practice with an upper extremity muscle of the dominant right hand while viewing the mirror image of the active limb. The forward model, proposed by Iacoboni et al. [3,8], mediates the practice effects through the path, denoted by the *solid lines*, starting in the 'involved' left primary motor cortex-left superior parietal lobe-corpus callosum and ends in the 'non-involved' right superior temporal sulcus. The inverse model, also proposed by Iacoboni et al. [3,8], produces cross-education through the path denoted by the *dashed lines*, starting in the 'non-involved' right hemisphere's superior temporal sulcus-corpus callosum-'involved' left superior parietal lobe-left premotor areas-left primary motor cortex. The inverse model, acting as the controller, retrieves the motor plan needed to complete the motor task. The forward model predicts the sensory outcome of the motor plan. Information from the forward model updates the inverse model [3,8]. Alternative and additional paths involve interhemispheric connections transferring activation from the 'involved' to the motor areas in the 'non-involved' hemisphere, denoted by the *dotted lines*, assigning a role of the ipsilateral hemisphere in evoking cross-education. The model presents the visual input, *thin solid line*, in the right hemisphere only because imaging studies show that the left superior temporal sulcus (i.e., core element of the mirror-neuron system involved in processing visual information) is inactive during mirror training with the right hand. The map is displayed as left hemisphere on the left and right hemisphere on the right. *Shaded areas* denote the regions of the brain involved in the mirror-neuron system and in mediating cross-education. *Darker shading* denotes more definitive evidence. Evidence for the involvement of structures in the left hemisphere: dorsal premotor cortex [19]; ventral premotor cortex [19,81]; supplementary motor area [81,83]; primary motor cortex [19,52,83,84]; somatosensory cortex [19]; inferior parietal lobe [81]; superior parietal lobe [19]; cerebellum (outside) [83]; occipital cortex [83]; medial occipital gyrus [19]. Evidence for the involvement of structures in the right hemisphere: dorsal premotor cortex [81]; primary motor cortex [20,52,58,83]; superior temporal sulcus [19]; middle temporal gyrus [19]; cerebellum (vermis 4/5/6) [19]; superior occipital gyrus [19]; occipital cortex [83].

and extend these data by varying task complexity, intensity, sensory input, and direction of transfer.

It remains to be seen if the unilateral motor practice in cross-education studies with and without a mirror would produce Hebbian associations in the implicated neural structures and mediate the cross-education effects. There is evidence that the MNS plays a causal role in generating imitative behaviour through sensorimotor learning [86] and it is possible that motor improvements after unilateral motor practice transfer to the non-practiced side by Hebbian associations. Indeed, there is some preliminary evidence to suggest that interhemispheric transfer of paired associative stimulation-induced plasticity occurs in the human M1 [87] and this transfer is associated with reduced IHI, an adaptation that also occurred after chronic unimanual motor practice [13].

2.4. Clinical implications

Considering that almost every cross-education study recommended the inclusion of unilateral motor practice in rehabilitation of patients suffering from unilateral conditions, the clinical benefits of cross-education have been widely claimed but the presumed benefits remain largely unexploited. One study stated that the magnitude of transfer is unlikely to have a meaningful effect in a clinical condition [14]. Initial studies were poorly controlled and the observed cross-education effects might have somewhat misleadingly heightened the expectations [88,89]. Recent studies have re-focused these research efforts and demonstrated feasibility and clinical benefits following cross-education interventions, so far mostly in healthy adults. A unilateral upper limb fracture represents a clinical condition where training the intact limb could mitigate a loss of strength and function through cross-education of the injured limb. Accordingly, immobilization of the left arm for three weeks coupled with strength training of the free, right, limb confirmed the so far untested clinical benefits of cross-education [18,79,90]. These studies have uniformly found a strength-loss sparing effect in the immobilized arm compared with strength loss in the control group's immobilized arm. Recent data demonstrated that unilateral strength training could improve rehabilitation outcomes after a fracture or other soft tissue injury requiring immobilization or movement restriction [91].

Individuals who suffered a stroke could also benefit from cross-education [92,93]. Small et al. [29] posited that practice in rehabilitation after a stroke should focus on ways to cure motor deficits (remediation) rather than circumvent them (compensation), which implies that training methods focusing on neural circuit reorganization should be implemented in stroke rehabilitation. In stroke, reduced IHI can lead to hyperexcitability of the M1 in the unaffected hemisphere and this hyperexcitability might be reduced due to cross-education because connectivity between both M1s is improved by unilateral strength exercises [13]. Michielsen et al. [93] found after six weeks of mirror training with the unaffected hand an improvement in upper-extremity motor functioning of the affected hand. Thereby, they observed a shift in activation balance from the unaffected to the affected M1 in the mirror training group only. Both studies strengthen the conclusion of Small et al. [29] that action observation has a positive additional impact on recovery of motor functions after stroke by reactivation of motor areas, which contain the MNS. If future studies do demonstrate that unilateral exercise of the non-paretic hand improves the function of the paretic hand then cross-education could be a new approach in stroke rehabilitation.

Although these initial studies are promising, future studies will have to examine if patients with a diagnosis of upper limb fracture exhibit similar strength sparing effects as healthy volunteers. A recent study in patients who suffered a stroke seven years earlier showed 31% and 34% increase in dorsiflexion strength, respectively, in the more and less affected limb after training the less affected limb for six weeks using maximal isometric dorsiflexion contractions [94]. Four participants who were unable to generate measurable force in the more affected limb prior to training were able to do so after training the less affected leg. Such positive effects of cross-education, currently not incorporating a mirror, also occurred in healthy adults using a more effective mode of strength training with eccentric compared with concentric strength training in stroke patients [36].

2.5 Recommendations

Imaging, EEG, and TMS studies comparing activation maps and excitability produced by unilateral motor practice with and without a mirror would increase our understanding about magnitude of overlap. Such information would improve our ability to target clinical dysfunction with a higher degree of specificity. There is a need to determine the effects of unilateral exercise with and without a mirror on performance outcomes in the resting hand. Future studies should quantify if task complexity of unilateral exercise interacts with the use of a mirror in the amount of cross-education. New studies must consider the interaction between injury and the efficacy of transfer with and without a mirror. Although cross-education seems to be more effective from the dominant right to non-dominant left limb in healthy individuals [9,13,18,50,78,79], cross-education was effective regardless of the side of fracture [91]. Considering the magnitude of transfer seems to be greater with unilateral eccentric muscle contractions in healthy adults and also in stroke patients, there is specific need to examine the effects of task specificity of transfer with and without a mirror. The application of this approach can be relevant to individuals recovering from fractures [91], anterior cruciate ligament reconstruction surgeries[95,96], arthroplasty, fibromyalgia, arthritis, and traumatic injuries to demonstrate the strength-sparing effect in pathological conditions instead of healthy individuals wearing a cast or splint.

2.6 Conclusion

Imaging, EEG, MEG, TMS, neuroanatomical, and behavioral studies suggest that the MNS may be involved in cross-education and that the use of a mirror in cross-education studies could increase the transfer effect. The potentiating effect is most likely due to the activation of brain areas that are directly and indirectly involved in cross-education through the illusion created by the mirror image of the active limb being superimposed on the non-active limb behind the mirror. Mirroring reduces the inherent complexities of movement imitation and activates neural pathways that enhance cross-education by creating an illusion of movement.

There is still a substantial gap in our understanding as to how the homologous contralateral muscles after unilateral training are able to effectively exploit the extra brain activation to allow healthy individuals and patients to generate more force. It is also unclear how unilateral motor actions with or without a mirror give rise to bilateral brain activation. This may be due to concurrent activation of specific areas in the two hemispheres as suggested by EEG and imaging studies or, as proposed recently [73], due to the concurrent activation modified by interhemispheric influences, quantified by TMS studies. Regardless of the mechanism and initial skepticism [14], there is now accumulating clinical evidence that cross-education interventions can produce meaningful and functionally significant benefits for patients afflicted with orthopedic [91,95,96] and neurological conditions [94]. The present review proposes that a combination of cross-education with mirror training can further accelerate functional recovery.

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